

Case of Thrombosis of Rare Localization in a Cancer Patient with Combined form of Thrombophilia

Vorobev A, Makatsariya A*, Bitsadze V, Khamani N, Udovychenko M and Andreeva M

Department of Obstetrics and Gynecology, First Moscow State Medical Sechenov, University of the Ministry of Health Russian Federation, Russia

Abstract

Thrombosis can be a clinical symptom of hidden cancer, as evidenced by numerous studies. Inherited and acquired thrombophilia are well-known risk factors for venous thromboembolism. The incidence of thrombotic events in cancer patients is increased compared to normal population. Data on inherited thrombophilia and cancer is limited. In most cases, a key role in the pathogenesis of thrombosis of rare localization is played by hereditary thrombophilia. Clinically, venous thromboembolism and cancer are almost always closely interrelated, and often thrombosis can be the only clinical symptom of latent cancer. Here in this case report, we present a case of thrombosis of rare localization in a cancer patient with combined form of thrombophilia.

Keywords: Cancer; Hypercoagulation; Hereditary thrombophilia; Thrombosis

Introduction

Thrombosis can be a clinical symptom of hidden cancer, as evidenced by numerous studies [1]. Mechanisms of development of hypercoagulation in patients with malignant tumors include common factors associated with the response of organism to tumor (inflammation, acute phase reaction, dysproteinemia, focal necrosis, hemodynamic disorders) and more specific factors expressed by tumor cells and tumor-associated macrophages: Procoagulant factors, fibrinolytic activity of cancer cell interacted with platelets, mononuclear macrophages, endothelium and process of tumor neoangiogenesis [2,3]. In most cases, a key role in the pathogenesis of thrombosis of rare localization is played by hereditary thrombophilia. Thus, in the general population, thrombosis of this localization is an extremely rare pathology (0.01% according to autopsies in patients in the surgical hospital), whereas in patients with AT III deficiency, mesenteric thrombosis develops in 10% of cases, with protein C deficiency in 6%, and with a deficiency of protein S-in 4% of cases. Also, the manifestation of APS leads to thrombosis of rare localization [4].

Case Presentation

Patient N is a 36-year-old female admitted the surgical hospital with complaints of pain in the lower abdomen, a positive symptom of irritation of the peritoneum, sub-febrile temperature and also, she felt pain when pressing on the appendix area. In blood tests, leukocytosis was detected with a shift of the leukocyte formula to the left. With the diagnosis of acute appendicitis, the patient N was urgently performed laparoscopy, but an intact appendix was found. A revision of the abdominal cavity was performed: Edematous cyanotic fallopian tube was found on the right side, with no signs of torsion of the ovarian cyst, a slightly enlarged and moderately painful uterus. A routine coagulogram was performed, which did not reveal any significant changes. With the diagnosis of acute endometritis, acute salpingo-oophoritis patient N was transferred to the gynecological department of the hospital. Pelvic CT was performed: Thrombosis of the ovarian vein on the right, thrombosis of the right common iliac vein, increase in parametrical and common iliac lymph nodes, and the presence of a tumor without clear boundaries in the uterus.

Endometrial aspiration biopsy was performed with thrombolytic

therapy and anticoagulation therapy with LMWH, obtained result: low-grade adenocarcinoma. With the diagnosis of low-grade adenocarcinoma of the uterus T2N1M0, thrombosis of the right iliac and right ovarian vein, patient N was transferred to the oncogynecology department. Against a background of ongoing anticoagulant therapy, a hysterectomy operation with lymphonodectomy (Wertheim's operation) was performed, vascular surgeons carried out placement of vena cava filter. During the operation blood loss was 1200 ml, an infusion of 400 ml of plasma, 1200 ml saline infusions were carried out.

In 8 hours after the operation, LMWH (Enoxaparin Sodium 40 mg, 10.4 ml) was prescribed once a day for the first two days. Then, on the 3rd day a dose 0.6 ml of Enoxaparin Sodium was prescribed for 4 weeks. Then she was prescribed Rivaroxaban (Ksarelto) 20 mg 1 time a day. Anticoagulant therapy was prescribed for 3 months with dose control according to the anti-Xa factor and the level of D-dimer in the blood. Also, Dipyridamol (Kurantil) at a dose of 25 mg 3 times a day was prescribed.

From the past history, it was found out that patient N had 5 pregnancies: the first was in 23 years old and ended with spontaneous abortion at an early period of 6-8 weeks, the second pregnancy in 25 years old accompanied by the threat of interruption from an early period, proceeded with pre-eclampsia and signs of feto-placental insufficiency, premature birth with a live newborn weighing 2500 kg at 35 weeks of pregnancy. On the 5th day after childbirth, patient N noted blurred vision and a narrowing of the field of view on the left, which was seen as a transitory change associated with increased blood pressure against a background of preeclampsia. Special treatment for patient N was not prescribed. Subsequently, patient N was recommended hormonal contraception, on the background of which, after 5 months of use venous thrombosis of the right shin was developed, a course

*Corresponding author: Makatsaria A, Department of Obstetrics and Gynecology, First Moscow State Medical Sechenov, University of the Ministry of Health Russian Federation, Russia, Tel: 74957885840; E-mail: gemostasis@mail.ru

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of thrombolytic and anticoagulant therapy was conducted, which exactly is difficult to specify. After that patient N used barrier methods of contraception, subsequent pregnancies in 29, 32 and 33 years old ended by medical abortion. The last abortion was complicated by acute endometritis, salpingo-oophoritis, against a background of incomplete interruption.

Due to the complicated obstetric-gynecological history, she preferred not to be observed by gynecologist, did not pay attention to periodic discharge from the genital tract, she did not visit the gynecologist for the last 3 years after the last abortion. From a family history: mother suffers from chronic recurrent thrombophlebitis of the lower extremities, was operated for varicose disease of the lower extremities. Grandmother from the mother's side also suffered from thrombophlebitis. Father of patient N suffered 2 episodes of myocardial infarction. We have carried out an investigation to identify the genetic and acquired forms of thrombophilia. Combined form of thrombophilia was found: the circulation of antiphospholipid antibodies in high titer (more than 80 GPL), a number of genetic forms of thrombophilia were also found: the heterozygous mutation of Factor V Leiden, as well as the homozygous form of Methylenetetrahydrofolate reductase gene mutation (MTHFR) C677T. Also, hyperhomocysteinemia was detected up to 36 mmol/l, confirmed in 2 laboratory tests with an interval of 12 weeks.

Discussion

Clinically, venous thromboembolism and cancer are almost always closely interrelated, and often thrombosis can be the only clinical symptom of latent cancer- as it was in the case of patient N. In the process of tumor progression, the masking of malignantly transformed cells from the effectors of the immune system is ensured by the presence of a fibrin barrier. Fibrin fibers are always present in any tumor tissue, which is particularly characteristic of the active zone of proliferation of malignant cells. A powerful fibrin barrier is formed due to distortion of the processes of permanent stimulation of fibrinogenesis and concomitant fibrinolysis in the tumor zone [5,6]. From the side of tumor cells, the initiating effect on the components of the hemostasis system and the process of fibrin formation is mediated by macrophages present in the tumor zone, whose reaction to malignant cells is expressed by increased production of proinflammatory cytokines, such as TNF α , IL-1, IL-6, IL-8 and other active molecules [7,8]. In the focus of tumor growth, the protective role of fibrin is distorted, and transformed cells use fibrin mesh as a mechanical barrier from the cells of the immune system.

In addition, in the structure of tumor tissue fibrin performs the function of extracellular matrix. Fibrin filaments have a stimulating effect on fibroblasts whose presence in the tumor is necessary to maintain the concentration of growth factors consumed by cancer cells and the secretion of components entering the stroma of the tumor tissue. Malignantly transformed cells use fibrin for their own purposes because of their ability to control the activity of the fibrinolytic components of hemostasis-plasmin system-tissue inhibitors-plasminogen activator.

The state of hypercoagulability in cancer is due to a complex of interactions of tumor cells and their products with the cells of the body. Tumor cells can directly activate the coagulation cascade, which leads to thrombosis or to exhibit procoagulant properties, or to inhibit the anticoagulant system of the endothelium, platelets, monocytes, macrophages. Tumor masses cause, at least, a local stasis, caused by the invasion of the tumor into the blood vessels, by mechanical compression of the tumor mass [9-11].

Many diseases can aggravate the course of the tumor process and further stimulate the hemostatic system, which can lead to thromboembolic conditions. The main diseases that significantly worsen the prognosis of the malignant process and increase the risk of developing thrombotic complications include:

1. Cardiovascular diseases: Ischemic heart disease, hypertension, atherosclerosis
2. Vascular pathology: Systemic diseases affecting mainly the bloodstream, diabetes mellitus
3. Systemic diseases of connective tissue
4. Diseases of the liver and kidneys
5. Endocrine diseases

Family risk factors for cardiovascular disease (recurrent myocardial infarction in father) and vascular pathology in mother and grandmother of the patient N were found. However, the most thrombogenic comorbid condition is APS and genetic forms of thrombophilia, which was revealed in more in-depth examination. Against a background of the detected multiple genetic factors of thrombophilia, especially in combination with the circulation of antiphospholipid antibodies in patient N, it is possible to raise the question of the correct assessment of the situation with blurred vision and a narrowing of the visual field on the left, which patient N noted on the 5th day after second delivery. Most likely, it could be an unrecognized retinal vein thrombosis, which occurred against the background of pre-eclampsia, which is also a consequence of the development of thrombophilia. Also, a significant anamnestic factor that may indicate the presence of genetic and acquired factors of thrombophilia in patient N may be an episode of venous thrombosis of the right shin, which developed with the use of hormonal contraception. However, even then the hemostasiogram was not made, which could indicate the presence of a changes in the levels of TAT, F1+2, D-dimer, and also to determine the presence of circulating antiphospholipid antibodies. In particular, patient N was diagnosed a heterozygous Factor V Leiden mutation and a homozygous form of the Methylenetetrahydrofolate reductase (MTHFR) gene mutation C677T. The consequence of Factor V Leiden mutation are disorders of the protein C system, representing an important natural anticoagulant pathway. Normally, APC inhibits coagulation by cleavage of peptide bonds in FV/Va and VIII/VIIIa. APC-dependent cleavage of FVa is stimulated by protein S, whereas for the inactivation of FVIII a synergistic interaction of APC, protein S and proteolytically modified by APC factor V is needed [12-14]. FVa increases the activation of protein C by 50 times under the action of the thrombomodulin-thrombin complex. Thus, normally FV mediates two opposite functions: procoagulant-after conversion from inactive form V to active form Va under the influence of FXa and thrombin, and anticoagulant-after cleavage under the action of APC. In addition, FVa simultaneously activates coagulation and the formation of the most important anticoagulant APC, which in turn, contributes to the degradation of FVa. Such mechanism of regulation by negative feedbacks between components of the procoagulant and anticoagulant system serves to limit the spread of thrombosis processes. Factor V Leiden mutation has a double effect: It is not only the cause of the violation of factor Va degradation by APC but also the degradation of factor VIIIa. The proteolysis of the thrombin-activated, phospholipid-linked factor V Leiden differs from the proteolysis of the normal molecule. As a consequence, FVa, formed as a result of thrombin FV activation, persists longer on the membrane surface where it is ready to form prothrombinase complexes with FXa. As a result, the formation of thrombin increases, activation of FV and FVIII

also increases, which leads to hypercoagulability. Reflection of this is an increase in the level of fragments of activation of prothrombin (F1+2) and complexes of thrombin-antithrombin in plasma in patients with inherited APC-resistance. APC retains the ability to cleave mutant FV, although much more slowly than normal. Perhaps this ability of Protein C partially protects carriers of the FV Leiden mutation from the onset of thrombosis. In addition to influencing the cofactor activity of factor V, the Leiden mutation also has effects on the fibrinolytic properties of factor V, which is manifested by slowing down of fibrinolysis processes. At the present time, the profibrinolytic properties of APC are well known. It was shown that 10 times more APC is required to shorten the lysis time of the clot containing the V Leiden factor from 140 min to 50 min than for lysis of the clot containing normal factor V according to Cooper et al. in 1997. However, in the absence of a thrombin-activated fibrinolysis inhibitor (TAFI), APC does not affect either the lysis of the clot containing the Leiden factor V nor the lysis of the clot containing normal factor V. TAPI is activated by the thrombomodulin-thrombin complex. TAPI, which is a pro-carboxypeptidase B, cleaves terminal residues from fragments of fibrin. Thus, TAPI prevents binding of plasmin and t-PA to fibrin and reduces the intensity of fibrinolysis processes. Thus, the violation of the fibrinolytic response to APC in patients with FV Leiden is TAPI-dependent. This phenomenon is one of the important mechanisms of the prothrombotic tendency in patients with the FV Leiden mutation [15-17]. Hyperhomocysteinemia affects many mechanisms involved in thrombus formation, including coagulation cascade, vascular-platelet link, redox reactions, endothelium, smooth muscle cells of vessels. An increased level of homocysteine leads to an increase in the level of TF in the blood plasma- A key protein of the internal coagulation cascade, which is especially important in combination with the oncological process, as TF is one of the main procoagulant factors of tumor tissue. Homocysteine inhibits natural anticoagulant mechanisms, preventing the binding of antithrombin III to heparan sulfate, which is part of the endothelium, by blocking the interaction of membrane protein of thrombomodulin with thrombin, which is necessary for the activation of protein C [18,19].

Also, homocysteine reduces the number of binding sites of annexin II with t-PA, which leads to disruption in the conversion of plasminogen to plasmin and a reduction in fibrinolytic activity. In addition, homocysteine changes the metabolism of arachidonic acid in platelets, which leads to a 30% to 40% increase in the synthesis of thromboxane A₂.

In general, the process of tumor growth is accompanied by an increase in some circulating coagulation factors: factor V, fibrinogen, von Willebrand factor, markers of thrombophilia, prothrombin fragments 1+2 and D-dimer, damage the function of endogenous anticoagulants; Decreased levels of natural anticoagulants-antithrombin III and protein S. In fact, the process of chronic intravascular coagulation of blood is induced in parallel [20].

Returning to the diagnostic search at the stage of primary diagnosis, patient N was given a routine coagulogram, which, even against the background of an extensive thrombosis, did not reveal any significant changes. Indeed, coagulation indicators cannot show a tendency to develop thrombosis in any way, but only the risk of bleeding. In the case of patient N, if hemostasiogram was performed on time, the risk of thrombosis would be assessed adequately and, with CT performed on time, it would be possible to avoid the spread of thrombosis in the common iliac vein. The key position in launch of the coagulation cascade through the vascular-platelet mechanism of hemostasis is occupied by

a tumor cell:platelets circulating in the blood in the inactive state are included in the complexes "platelet-tumor cell" and undergo a number of morphological and biochemical changes in the presence of cancer cells, while specific glycoproteins on the surface of platelets can bind fibrinogen, fibrin, von Willebrand factor (vWF), which initiate their adhesion and aggregation, lead to increased incorporation of platelets into fibrin clots and thrombi, which makes the latter more resistant to fibrinolysis [21]. In addition, tumor cells are able of synthesize ADP. While collagen and thrombin promote platelet secretion, ADP is the most important agent by which a platelet activates itself. ADP promotes changes in the form, degranulation and aggregation of platelets. The result of the activation of coagulation is the deposition of fibrin on the surface of tumor tissue.

Thus, platelets are the most involved component of the hemostatic system in the presence of malignant neoplasm, participating both in the protective reactions of the body to limit the spread of the tumor, and promoting angiogenesis, tumor growth and metastasis [22].

In general, the process of metastasis and tumor growth can be divided into the following stages:

1. Adhesion of a tumor cell to platelet and platelet activation.
2. Activated platelets generate thrombin on the surface, which can stimulate the adhesion of tumor cells to platelets and endothelium, as well as tumor growth.
3. Tumor cells in a complex with platelets significantly better survive in the bloodstream.
4. Platelet embolism with tumor cells cause ischemic damage of endothelium in the lower areas of vessels, which leads to stimulation of the adhesive properties of endothelium.
5. Activated platelets in close contact with tumor cells secrete mediators that increase the permeability of the vascular wall, thereby facilitating the invasion of the tumor cell.
6. Platelet growth factors can support tumor growth in the focus of metastasis.
7. Platelets, as a source of angiogenesis factors, contribute to the process of neoangiogenesis in metastatic focus.

Conclusion

Thus, with early detection of genetic forms of thrombophilia in combination with circulating antiphospholipid antibodies and timely prescribing of anticoagulation therapy, it would be possible to avoid such extension of oncological process. This once again indicates the need for a thorough study of family and personal history, and in the process of diagnostic search to take into account the possible risks of thrombotic complications.

In patient N, a combined form of thrombophilia was found, which often leads to thrombotic complications. In the presence of a locally advanced malignant neoplasm, patient N refers to a group of extremely high risk for the developing thrombotic complications.

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